REMARKS

Upon entry of this amendment, claims 1, 60, 65, 67, and 69-72 are pending in the application. In this response, claims 2, 3, 56-59, 61-64, 66, and 68 have been cancelled. The amendments to claims 60 and 65 are supported by the claims as originally filed. Support for new claims 69-72 appears at least in the claims as originally filed. In addition, new claim 69 is supported by disclosure at page 21, lines 26-30, new claim 70 is supported by disclosure at page 10, line 28, new claim 71 is supported by disclosure at page 54, lines 5-9, and new claim 72 is supported by disclosure at page 57, lines 28-29.

The title has been amended to more clearly describe the invention elected in the March 18, 2002 Response to Restriction Requirement.

The specification has been amended to remove the browser-executable code at page 11, lines 17 and 20, and at page 12, line 25 so that the web sites are referred to by a non-executable name only.

No new matter has been added.

Rejection under 35 U.S.C. § 101:

The Examiner rejects claims 1-3 and 56-68 as unpatentable for lack of either a specific, substantial, and credible asserted utility, or a well-established utility. The Examiner's position is that "[n]o well-established utility exists for newly isolated complex biological molecules." (See Office Action, page 4). Applicants traverse the rejections as applied to the newly pending claims.

Applicants respectfully assert that the polypeptides of the present invention have a specific, substantial, and credible utility, and therefore are patentable under 35 U.S.C. §101. Applicants assert that the claimed proteins can be used, *inter alia*, as a marker for cell proliferation diseases, including central nervous system (CNS) cancer (glio/astro and neuro; metastasis), lung cancer (non small cell), breast cancer, colon cancer, ovarian cancer, kidney cancer (clear cell type), prostate cancer, and thyroid cancer. *See* specification at page 95, lines 4-8. SEQ ID NO:4 shows a relatively high level of expression in these tissues. *See* specification at Tables 4 and 5. Such a high expression level in these cell lines demonstrate that SEQ ID NO:4 can be used as a diagnostic marker for screening purposes, and also could be used to monitor the progress or stage of the disease when it has not metastasized. Applicants respectfully assert that such markers have a real world use and patentable utility.

The polypeptides of the present invention are characterized as members of the Neuromedin family of proteins based on homology. On page 11 of the instant Specification, Applicants disclose that the polypeptides of the present invention share 88% identity over the entire sequence with a human neuromedin B-32 precursor protein. The Utility Examination Guidelines state that "when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." Fed. Reg., Vol. 66. No. 4, January 5, 2001, p. 1096. There is a well-established utility for neuromedin B-32 as a smooth-muscle stimulating peptide. *See* Minamino *et al.*, Peptides, 6 Suppl 3:245-8 (1985).

One of ordinary skill in the art accepts structural homology based on amino acid sequence identity as a credible method of determining the function of a polypeptide. *See* Henikoff *et al.*, Science, 278:609-614 (1997). Accordingly, based on the evidence presented in this response that SEQ ID NO: 4 shares a high degree of homology with members of the Neuromedin family of proteins, one skilled in the art would assign a function to SEQ ID NO: 4 based on the function of those polypeptides with which it shares significant homology. Furthermore, it was well known in the art at the time this application was filed that some members of the neuromedin family of proteins contained a highly conserved bombesin-like peptide consensus sequence, W-A-x-G-[SH]-[LF]-M, as a signature mark for inclusion in this protein family. (*See* PFAM database). This conserved region appears between amino acid residues 40-46 in SEQ ID NO: 4. Thus, one skilled in the art would also attribute SEQ ID NO: 4 to have the corresponding functions of the neuromedin family of proteins, and hence the same utility.

The neuromedin family of proteins are known to those skilled in the art to function as smooth-muscle stimulating peptides. The Utility Examination Guidelines further state that "when a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein." Fed. Reg., Vol. 66. No. 4, January 5, 2001, p. 1096. The sequences of members of the neuromedin family are sufficiently conserved, thereby imputing the same utility to a novel member of their protein class, such as SEQ ID NO 4. Moreover, the polypeptide of the invention

is more identical (88%) to human neuromedin B at the amino acid level than the nearest family member, *R. norvegicus* (rat) neuromedin B precursor (71% over 114 amino acids). *See* specification at page 11, lines 17-19. Therefore, it is more than reasonable to assign SEQ ID NO:4 to the neuromedin family and to impute the known function as a smooth-muscle stimulating peptide to the polypeptide of the invention.

Consistent with the teachings of the specification and the utilities known by those of ordinary skill in the art, Applicants respectfully submit that it is clear that the polypeptides of the present invention can be used as markers for cell proliferation disorders, i.e., credible, specific and substantial utilities. Applicants request withdrawal of the rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. § 112, ¶ 1 (How to Use):

Claims 1-3 and 56-68 have been rejected under § 112, ¶ 1, because one of ordinary skill in the art would allegedly not know how to use the invention since the claimed invention was said to lack utility. Applicants have disclosed the sequence on which the newly claimed subject matter is based. Further, one of ordinary skill in the art would know how to make the claimed invention based on the disclosed sequence. As described above, the sequences of the pending claims have a specific, substantial and credible utility as markers for cell proliferation disorders. Because the claims have such utility, Applicants submit that they are enabled. Thus, this rejection of these claims should be withdrawn.

Rejection under 35 U.S.C. § 112, ¶ 1 (Enablement):

On page 10 of the Office Action, the Examiner rejects claims 2-3, 56-59, and 61-66 as unpatentable, because the subject matter described in the Specification allegedly does not enable one skilled in the relevant art to make and/or use the claimed invention. In particular, the Examiner asserts that "[t]he scope of the patent protection sought by the Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification . . . ". Specifically, the Examiner alleges that the instant application does not provide enabling disclosure for polypeptide variants that are at least 90% identical to SEQ ID NO: 4.

Without acceding to the propriety of the Examiner's position, and solely to expedite prosecution, Applicants have amended the claims so that they no longer read on variants that are at least 90% identical to SEQ ID NO: 4. The newly pending claims are directed to various

embodiments of neuromedin-like polypeptides comprising and consisting of SEQ ID NO:4. Accordingly, Applicants submit that the "how to make" prong of enablement has been met. The Examiner also asserts lack of enablement based on the "how to use" prong of the enablement requirement. Applicants respectfully submit that the Specification does teach how to use SEQ ID NO:4. Applicants reiterate that the data presented in the specification as filed indicate that the polypeptide given by SEQ ID NO:4 can be used as markers for diagnosing cell proliferation disorders.

In view of the foregoing reasoning, Applicants respectfully submit that the newly pending claims meet the enablement requirement of 35 U.S.C.§ 112, ¶ 1. Reconsideration and withdrawal of the rejection on this basis is respectfully requested.

Rejection under 35 U.S.C. § 112, ¶ 1 (Written Description):

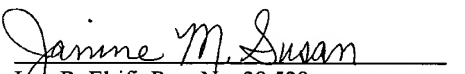
The Examiner rejects claims 59 and 65 as unpatentable for failing to meet the written description requirement. The Examiner's position is that there is not sufficient written description of an entire genus consisting of allelic variants of polynucleotides encoding functionally equivalent polypeptides. Applicants have cancelled claim 59. In order to expedite prosecution of this application, Applicants have amended claim 65 so that it no longer refers to allelic variants encoding SEQ ID NO: 4. The pending claims now recite various embodiments of an amino acid sequence of SEQ ID NO:4, or at least 99% identical to SEQ ID NO:4. Applicants submit that Figure 3B of the specification, which discloses SEQ ID NO:4 meets the written description requirement. In view of the above reasoning, Applicants respectfully request reconsideration and withdrawal of the rejection as it is applied to the new claims.

CONCLUSION

A full response has been made to each of the Examiner's rejections or objections. Accordingly, Applicants submit that the application is in condition for allowance and such action is respectfully requested. Should any questions or issues develop during review of the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below. No fee is believed to be due, however, the Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 15966-609 (Cura-109).

Respectfully submitted,

Dated: December 18, 2002



Ivor R. Elrifi, Reg. No. 39,529
Naomi Biswas, Reg. No. 38,384
Janine M. Susan, Reg. No. 46,119
Attorney for Applicants
c/o MINTZ, LEVIN, COHN, FERRIS
GLOVSKY AND POPEO, P.C.
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

Marked-up version showing the changes made

Because of the use of underlining and square brackets (*i.e.* []) in the text of the specification, the changes made to the specification are indicated by a pair of dashes (*i.e.* --) flanking text to be added and non-square brackets (*i.e.* {}) flanking text to be deleted.

In the Title:

Replace: {NOVEL PROTEINS AND NUCLEIC ACIDS ENCODING THE SAME} with: --HUMAN NEUROMEDIN PROTEIN--

In the Specification:

Change the paragraph beginning on page 11, line 11, as follows:

The NOVNEUR protein disclosed has substantial homology to both human neuromedin B-32 precursor and rat neuromedin B precursor (*see* Figure 5). NOVNEUR is 88% identical to human neuromedin B precursor at the amino acid level, over residues {-}6 to 112 {of} of SEQ ID NO: 4. NOVNEUR shares the bombesin-like peptide family consensus sequence, W-A-x-G-[SH]-[LF]-M (where positions 5 and 6 are His-Phe in NMB, ranatensin, and NOVNEUR (*see* residues 40-46 of SEQ ID NO: 4) shared by all putative members of this family (*see* PFAM database at {www. sanger.ac.uk}-- sanger.ac.uk website --). The NOVNEUR polypeptide of the invention is more identical (88%) to human NMB at the amino acid level than the nearest family member, *R. Norvegicus* (rat) NMB precursor (71% over 114 amino acids)(*see* UniGene database, {www. ncbi.nih.gov/UniGene}-- ncbi.nih.gov/UniGene website --).

Change the paragraph beginning on page 12, line 18, as follows:

The NOVGON protein disclosed has homology to a number of species variants of the gonadotropin family, including goldfish gonadotropin, and bovine and sheep lutropin (*see* Figure 8). NOVGON is 61% similar to carp gonadotropin beta chain precursor at the amino acid level, over residues 42 to 126 of SEQ ID NO: 6. The NOVGON polypeptide of the invention is comparably as similar (61%) to carp gonadotropin beta chain precursor at the amino acid level as the nearest family member, *R. Norvegicus* (rat) LSH beta-chain precursor, is to human choriogonadotropin beta-chain (65% identical over 164 a.a.) (*see*UniGene database, {www. ncbi.nlm.nih.gov/UniGene}-- ncbi.nlm.nih.gov/UniGene website --). The protein also is

significantly similar to human gonadotropin/bLH chimera, D10 (patp: R15106) (57% at the amino acid level) and Equine chorionic gonadotropin beta-chain protein (patp: R65110) (51% at the amino acid level). See Fig. 7B.

Change the paragraph beginning on page 13, line 28 as follows:

The NOVINTRA A protein disclosed has substantial homology to both human IL-1 delta encoding DNA and intracellular IL-1 receptor antagonist type II, as well as ovine IL-1 beta (*see* Figure 11). NOVINTRA A is 62% similar to mouse IL-IL1 protein at the amino acid level, over residues 4 to 152 of {of} SEQ ID NO: 8. The NOVINTRA A polypeptide of the invention is comparably as similar (62%) to human IL1RN at the amino acid level as the nearest family member, *M. musculus* (mouse) intracellular IL1RN, is to human IL1RN (75% identical over 157 a.a.) (see UniGene database, {www.ncbi.nlm.nih.gov/UniGene}-- ncbi.nlm.nih.gov/UniGene website --). The protein also has substantial similarity to human delta interleukin-1 like protein 1 (SPTREMBL-ACC:19UBH0)(59% at the amino acid level). Smith et al., J. Biol. Chem. 275: 1169-1175 (2000). See Fig. 10B.

Change the paragraph beginning on page 14, line 27 as follows:

The NOVINTRA B protein disclosed has substantial homology to both human intracellular IL-1 receptor antagonist {tyte}-- type -- II and ovine IL-1 beta (*see* Figure 14). NOVINTRA B is 51% similar to human IL1RN homolog at the amino acid level, over residues 25 to 170 {of of one} of SEQ ID NO{s}: 10, 100% identical to human FIL-1, a member of the IL-1 superfamily, over residues 21 to 170 of SEQ ID NO: 10, and 94% identical to human IL-1 homolog 2 over residues 21 to 106 of SEQ ID NO: 10. The NOVINTRA B polypeptide of the invention is comparably as similar (51%) to human IL1RN at the amino acid level as the nearest family member, *M. musculus* (mouse) intracellular IL1RN, is to human IL1RN (75% identical over 157 a.a.) (*see* UniGene database, {www.ncbi.nlm.nih.gov/UniGene} -- ncbi.nlm.nih.gov/UniGene website --).

In the Claims:

Cancel claims 2, 3, 56-59, 61-64, 66, and 68.

Amend the claims as follows:

60. (Amended) An isolated polypeptide comprising [the amino acid sequence of] a mature form of the amino acid sequence of SEQ ID NO:4.

65. (Amended) The isolated polypeptide of claim [61] 60, wherein the [amino acid sequence is a naturally-occurring allelic variant of] mature form [of SEQ ID NO:4] is naturally occurring.

Add the following new claims:

--69. (New) An isolated polypeptide comprising an amino acid sequence that is at least 99% identical to the amino acid sequence of SEQ ID NO:4.

70. (New) The polypeptide of claim 1, wherein the polypeptide is a human polypeptide.

71. (New) A composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier.

72. (New) A kit comprising, in one or more containers, the composition of claim 71.--